GeneAssist™ Pathway Atlas

Mechanism of Botulinum Toxin Overview

Botulinum neurotoxin (BoNT) is one of the most potent toxins that inhibit neurotransmitter release at the neuromusc is a microbial product synthesized by an anaerobic,gram-positive,spore-forming bacteria *Clostridium botulinum* whos In addition to *C. botulinum*,unique strains of *Clostridium baratii* and *Clostridium butyricum* also have the capacity to basis of the phenomenal potency of BoNT is enzymatic. The toxin is a zinc-dependent protease that cleaves one or m proteins by which neuronal vesicles release Ach (Acetylcholine) into the neuromuscular junction. This toxin acts prefe cholinergic nerve endings to block Ach release and is both an agent that causes disease (i.e.,botulism) as well as an to treat the disease (e.g.,dystonia). The ability of BoNT to produce its effects is largely dependent on its ability to pe intracellular membranes. Thus,the toxin that is ingested or inhaled can bind to epithelial cells and be transported to t (Ref.1).

There are 3 main clinical forms of botulism: food borne,intestinal and wound related. Food borne botulism occurs wh by the preformed BoNT is eaten. Intestinal botulism occurs when spores are ingested and reproduce in the gastrointe releases the toxin in situ (primary infection,secondary intoxication). Wound-related botulism occurs when anaerobic abscess allow germination of *C. botulinum* spores. Most of these cases originate in wounds contaminated with soil or intravenous drug users. Regardless of how the toxin gets into the gut,it must reach the general circulation for its leth manifest. Since the toxin is too large to pass through epithelial barriers by diffusion,it is actively transported through process by which this occurs involves receptor-mediated transcytosis that does not damage the gastrointestinal tract produces all seven known serotypes of the BoNT (A,B,CAlpha,CBeta,D,E,F and G),whereas *C. baratii* and *C. butyricu* serotype each (F and E,respectively). Each type is antigenically distinct with its own characteristics. BoNTs are secret polypeptide chain of about 150kDa each,which are cleaved endogenously or exogenously resulting into a 100 kDa he light chain linked through a disulfide bond (Ref.2). The botulinum toxin's mode of action involves three steps: extrac internalization,membrane translocation and intracellular substrate cleavage,and blockage of Ach release. The heavy the toxic action of BoNTs,cell surface binding (binding domain),and translocation across membranes (translocation d chain is responsible for the intracellular toxic activity. When the toxin reaches peripheral cholinergic nerve endings,th of membrane-penetrating events. Initially,the toxin binds to the surface of plasma membranes,and this is followed b endocytosis and pH-induced translocation across the endosome membrane. The receptor for BoNT at the neuromusc been unequivocally identified. However,a sialic acid-containing molecule,and possibly a ganglioside,is implicated in tc no consensus on the exact role played by this molecule. Once inside the low-pH endosome,the light chain dissociates and is released into the cytosol,where it acts as a zinc metalloprotease and cleaves SNARE (Soluble NSF-attachment proteins. Without functional SNARE complexes,the neurotransmitter Ach is not released into neuromuscular junctions myosin filaments. Blockade of transmitter release accounts for flaccid paralysis and autonomic dysfunction that is ch disease botulism. Although the toxin acts preferentially on cholinergic nerve endings,it does have the ability to block nerve endings as well. BoNT types-A and E act on SNAP25 (Synaptosomal-associated protein of 25 kDa); serotypes B VAMP (Vesicle-Associated Membrane Protein),also known as synaptobrevin; and serotype C acts mainly on Syntaxin, cleave SNAP25 (Ref.1). By disrupting neurotransmission at cholinergic junctions in the autonomic nervous system,th various forms of autonomic dysfunction. Its most life-threatening potential,however,is its ability to stop respiration b neurotransmission in diaphragm and intercostal muscles.

Patients with botulism typically present with difficulty seeing,speaking,and/or swallowing. Prominent neurologic findir botulism include diplopia,blurred vision,often enlarged or sluggishly reactive pupils,dysarthria,dysphonia,and dysphag appear dry and the pharynx injected because of peripheral parasympathetic cholinergic blockade. Sensory changes a for infrequent circumoral and peripheral paresthesias from hyperventilation as a patient becomes frightened by onset paralysis extends beyond bulbar musculature,loss of head control,hypotonia,and generalized weakness become prom persons,death results from airway obstruction (pharyngeal and upper airway muscle paralysis) and inadequate tidal and accessory respiratory muscle paralysis). Because botulism is intoxication,patients remain afebrile unless they ac secondary infection (e.g.,aspiration pneumonia). The toxin does not penetrate brain parenchyma; however,they ofte have communication difficulties because of bulbar palsies (Ref.3). Complications,such as eyelid ptosis,have been attr

(commonly referred to as Botox). An "hourglass" deformity,which is the consequence of temporalis muscle atrophy,h
In addition to acting as a toxin during botulism infection,Botox is also now being used to treat several disorders. Cars
very small doses of the toxin is used to treat two eye muscle disorders--uncontrollable blinking (blepharospasm) and
(strabismus) and a neurological movement disorder that causes severe neck and shoulder contractions,known as cer
Botox not only affects the neuromuscular junction directly,but also have intrinsic pain controlling effects by acting on
affecting pain perception. Recently Botox injection has come into vogue as a treatment for facial wrinkles. In the cou
wrinkles,it was discovered that people who suffered from migraines had a decrease in the frequency and severity of t
headaches. Additional studies are necessary in order to validate the effects of BoNT in the treatment of migraines. In
toxin has also proven to be a safe and effective therapy for a variety of somatic and autonomic motor disorders. Urol
clinical success with urethral and bladder Botox injections in the treatment of detrusor-sphincter dyssynergia,non-ne
spasticity,and refractory overactive bladder (Ref.5). The main treatment for severe botulism is meticulous supportive
include mechanical ventilation. To be most effective,the antitoxin must be given before much toxin has bound to pre
In cases of wound-related botulism,the wound must be debrided and therapy with an appropriate antibiotic such as p
Recovery takes weeks to months and occurs when new presynaptic end plates and neuromuscular junctions are form
used to reduce wrinkles and treat several disorders,BoNTs are also among the most lethal biological substances to h
a highly toxic aerosol form. New vehicles for transmission have emerged in recent decades,and wound botulism asso
heroin has increased dramatically since 1994. Such a potential bioterrorist threat necessitates the development of th
countermeasures against BoNTs.

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